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Abstract

Objective: In a prospective cohort study among 120,852 adult subjects the authors investigated the associations between cigarette, cigar, pipe, environmental tobacco smoking (ETS), and bladder cancer.
Methods: In 1986 all subjects completed a questionnaire on cancer risk factors. Follow-up for incident bladder cancer was established by linkage to cancer registries until 1992. The case–cohort analysis was based on 619 cases and 3346 subcohort members.
Results: Compared with lifelong non-smokers the age- and sex-adjusted incidence rate ratios (RR) for ex- and current cigarette smokers were 2.1 (95% CI 1.5–3.0) and 3.3 (95% CI 2.4–4.6), respectively. The RR for smoking duration was 1.03 (95% CI: 1.02–1.04) per 1-year increment. The RR per 10 cigarettes/day was 1.3 (95% CI 1.2–1.4). Tar and nicotine exposure increased bladder cancer risk only weakly. It appeared that associations of cigarette smoking characteristics with bladder cancer risk were largely attributable to cigarette smoking duration only. Smoking cessation, age at first exposure, filter-tip usage, cigar and pipe smoking, and ETS were no longer associated with bladder cancer risk after adjustment for frequency and duration of smoking.
Conclusions: The authors conclude that current cigarette smokers have a three-fold higher bladder cancer risk than non-smokers. Ex-smokers experience a two-fold increased risk. About half of male bladder cancer and one-fifth of female bladder cancer was attributable to cigarette smoking. Other smoking types (cigar, pipe, or ETS) were not associated with increased risks.

Introduction

Bladder cancer is the most common urologic cancer and is the seventh most common cancer among men, accounting for approximately 200,000 new cases per year worldwide. Bladder cancer is considerably more common in men than women (ratio worldwide is about 3.5:1). The incidence of this cancer varies worldwide; in general the highest incidence is observed in North America and Europe [1].

Narrative reviews, based on many case–control and follow-up studies, concluded that there is strong support for a positive association between various cigarette smoking characteristics and bladder cancer [2–11]. Cigarette smoking explains the occurrence of a greater proportion of bladder cancer than does any other known environmental factor [2]. In a recent systematic review of 43 epidemiologic studies, based on predominantly case–control data, we concluded that current cigarette smokers may have an approximately three-fold risk of bladder cancer compared with lifelong non-smokers [12].

However, the majority of earlier studies on cigarette smoking have presented the association between individual cigarette smoking characteristics on bladder cancer adjusted only for other environmental factors (*e.g.* diet, occupation). Although of interest, few studies simultaneously included different smoking characteristics in a regression model to estimate the individual impact of cigarette smoking features. The impact of active cigar and pipe smoking and environmental tobacco smoking (ETS) has also been evaluated less often than active cigarette smoking [13–25].

These findings prompted us to investigate the influence of cigarette, cigar, pipe, and ETS on the risk of bladder cancer in more detail in the ongoing Netherlands Cohort Study. In this follow-up study among 120,852 men and women, which started in 1986, detailed information has been collected on lifetime smoking history, including smoking status, frequency, age at first exposure, duration, cessation, inhalation, filter usage, tobacco brand, and ETS, by means of a self-administered questionnaire.

Materials and methods

Cohort

This population-based prospective cohort study on diet and cancer started in the Netherlands in September 1986. The cohort includes 58,279 men and 62,573 women aged 55–69 years at baseline. The study population originated from 204 municipal population registries throughout the country. The case–cohort approach was used for data processing and analysis [26]. Cases were enumerated from the entire cohort, while the accumulated person-years in the cohort were estimated from a subcohort sample. Following this approach a subcohort of 3500 subjects (1688 men and 1812 women) was randomly sampled from the cohort after the baseline exposure measurement. The subcohort has been followed up for vital status information. No subcohort members were lost to follow-up during the follow-up period. The study design, including data-collection strategies, has been described in detail previously [27].

Follow-up

Follow-up for incident cancer was established by record linkage to cancer registries and the Dutch national database of pathology reports [28]. The completeness of cancer follow-up was estimated to be over 96% [29]. The presented analysis is restricted to cancer incidence in 6.3 years of follow-up, from September 1986 to December 1992. After excluding prevalent cases with cancer other than skin cancer a total of 3346 subcohort members (1630 men and 1716 women) and 619 incident cases (532 men and 87 women) with microscopically confirmed, incident carcinomas of the urinary bladder, ureters, renal pelvis, or urethra were identified. Of these cases, 584 (94.3%) were diagnosed with bladder cancer of which 559 (95.7%) were transitional cell carcinomas. The morphologies of the remaining carcinomas were squamous cell (n = 3), adeno (n = 6), mixed (n = 1), or not specified (n = 15). Because the overwhelming majority of tumors occurred in the urinary bladder, and since the ureters, renal pelvis, and urethra are covered by the same urothelium as the urinary bladder, the term bladder cancer is used as a synonym for these neoplasms.

Questionnaire

At baseline all cohort members completed a self-administered questionnaire on risk factors for cancer. Tobacco smoking was addressed by questions on age at first exposure to smoking, age at last exposure to smoking, smoking frequency, inhalation, and smoking duration for cigarette, cigar, and pipe smokers. Furthermore, questions were asked about the cigarette brand most commonly smoked with or without filter-tip and the proportion of a cigarette actually smoked (using a visual analog scale). ETS was investigated using questions on smoking habits of parents and spouses, exposure to environmental smoke at work, and duration of exposure to ETS in private and occupational settings combined. The questionnaire data were key entered twice and processed in a standardized manner blinded with respect to case/subcohort status in order to minimize observer bias in coding and interpretation of the data.

Statistical analysis

Based on the questionnaire data we constructed, the following are variables on active cigarette, cigar, and pipe smoking: status (never, ex, current), frequency (cigarettes, cigars, or pipes per day), age at first exposure (years), duration (years), years since cessation (years), inhalation (yes/no), filter usage (filter, non-filter), and ETS: spouse smoking status (never, ex, current), parental smoking (yes/no), exposure to environmental smoke at work (high/low), and duration of exposure to ETS (hours/day). The continuous tobacco smoking characteristics were categorized into strata based on the distribution in the subcohort. We calculated the daily exposure to tar and nicotine for ever cigarette smokers from cigarette brand-specific information obtained from the Dutch Inspectorate for Health Protection, the Dutch Foundation on Smoking and Health, and the Dutch Foundation of the Tobacco Industry in combination with daily cigarette smoking frequency and the percentage of a cigarette actually smoked.

Incidence rate ratios (RR) and corresponding 95% confidence intervals (CI) for bladder cancer were estimated using exponentially distributed failure time re-

gression models [30] with the Stata statistical software package [31]. Standard errors were estimated using the robust Hubert–White sandwich estimator to account for additional variance introduced by sampling from the cohort. This method is equivalent to the variance–covariance estimator presented by Barlow [32] and by Lin and Ying [33]. Tests for dose–response trends in risk for bladder cancer over multiple categories were assessed by fitting ordinal exposure variables as continuous terms and performing likelihood-ratio tests between regression models with and without these variables. We confirmed constancy of the baseline hazard visually by plotting the natural logarithm of the baseline survival function against failure time.

The effect of active tobacco smoking and ETS was first evaluated by regression analyses after adjustment for age and sex and listwise deletion of missing smoking data. Based on earlier analyses [34–36], the following variables were subsequently considered as potential additional confounders: intake of alcohol (g/day); coffee (cups/day); tea (cups/day); water (ml/day); vegetables (g/day); and fruit (g/day); occupational exposure to dye, rubber, leather, or vehicle fumes (ever/never); and first-degree family history of bladder cancer (yes/no). Those variables that showed a more than 10% influence on the risk of bladder cancer when considered in a multivariable model were included as covariates in multivariable analyses. Unfortunately, information on other potential risk factors for bladder cancer (*e.g.* analgesic use, urinary tract infections, or drinking-water chlorination) was not available for this study. The adjusted incidence rate ratios of bladder cancer for cigarette, cigar, and pipe smokers compared with non-smokers are presented according to the different smoking features. Furthermore, we compared different regression models to identify the main predictors of bladder cancer, taking into account the changes in effect sizes and the contribution to the log-likelihood of the regression model. To prevent redundancy and collinearity, smoking status (current smoking *vs* ex/never smoking), smoking inhalation (yes *vs* no/never smoking), and filter usage (non-filter *vs* filter/never smoking) were recoded as indicator variables when they were simultaneously incorporated in one regression model with other smoking covariables. Based on the proportion of current cigarette smokers in the subcohort and the sex-specific age-adjusted RRs, we estimated the population-attributable risk of bladder cancer for men and women.

To ensure that the results were not influenced by changes in exposure by subjects with preclinical bladder cancer, we conducted analyses with and without cases diagnosed in the first 1–2 years of follow-up. The results from these analyses were similar; therefore analyses with all cases were presented.

Results

This distribution of bladder cancer cases and subcohort members according to age, sex, and tobacco product ever smoked is presented in Table 1. The age distribution among cases and subcohort members was comparable. Almost all men in our study population (96% of the cases, 90% of the subcohort members) and approximately half of the women (60% of the cases, 41% of the subcohort members) reported ever smoking cigarettes (Table 1). Among these, the prevalence of the ex-smokers was equal to the prevalence of the current smokers. Most men and almost all women never smoked

Table 1. Distribution – no. (percentage in parentheses) of bladder cancer cases and subcohort members according to age, sex, and tobacco product ever smoked; Netherlands Cohort Study (1986–1992)

	Cases		Subcohort	
	Men (n = 532)	Women (n = 87)	Men (n = 1630)	Women (n = 1716)
Age (years)				
55–59	119 (22.4)	29 (33.3)	620 (38.0)	651 (37.9)
60–64	207 (38.9)	29 (33.3)	568 (34.9)	583 (34.0)
65–69	206 (38.7)	29 (33.3)	442 (27.1)	482 (28.1)
Tobacco product				
Never smokers	20 (3.8)	35 (40.2)	159 (9.8)	1019 (59.4)
Cigarette	334 (62.8)	51 (58.6)	977 (59.9)	689 (40.2)
Cigar	7 (1.3)	0 (0.0)	37 (2.3)	0 (0.0)
Pipe	3 (0.6)	0 (0.0)	5 (0.3)	0 (0.0)
Cigarette, pipe	26 (4.9)	0 (0.0)	73 (4.5)	0 (0.0)
Cigarette, cigar	74 (13.9)	1 (1.2)	196 (12.0)	4 (0.2)
Cigar, pipe	6 (1.1)	0 (0.0)	18 (1.1)	0 (0.0)
All three products	59 (11.1)	0 (0.0)	162 (9.9)	0 (0.0)

a cigar or a pipe during their life. If a cigar or pipe were smoked, then it was most often combined with cigarette smoking. Cigarettes were more often smoked solely than in combination with other types of tobacco (Table 1).

The association between cigarette smoking and bladder cancer was similar in men and women for all cigarette smoking characteristics (p-interaction = 0.34, 0.79, and 0.81 for cigarette smoking status, frequency, and duration, respectively). Therefore, the results are presented for men and women combined. As is shown in Table 2, cigarette smoking clearly appeared to be associated with bladder cancer risk. The RR of bladder cancer was 3.3 (CI 2.4–4.6) for current cigarette smokers compared with never smokers. The sex-specific RRs were 3.7 (CI 2.3–6.0) and 2.4 (CI 1.4–4.1) for men and women, respectively. Stopping smoking appeared beneficial, although ex-smokers still experienced an increased RR of bladder cancer compared with lifelong non-cigarette smokers: 2.2 (CI 1.4–3.7) and 2.3 (CI 1.3–3.9) for men and women, respectively. Both the number of cigarettes smoked per day and the years in which cigarettes were smoked during a lifetime were associated with an increased risk of bladder cancer with statistically significant positive trends in risk. Age at first exposure and years since smoking cessation were negatively associated with the risk of bladder cancer (p-trend: 0.05 and <0.01, respectively) and inhalation increased this risk. The RRs associated with an increase in age at first exposure or years of smoking cessation were 0.98 (95% CI 0.95–1.0) and 0.96 (95% CI 0.95–0.98), respectively. It appeared that the use of filter-tipped cigarettes did not lower the risk of bladder cancer substantially compared with the use of non-filter-tipped cigarettes (Table 2). Additional adjustment for other non-smoking factors (*i.e.* alcohol, tea, coffee, water, vegetables, fruit, occupation, and family history) or active cigar and pipe smoking did not change the risk estimates for cigarette smoking. Based on the results of this study, we estimated that cigarette smoking might account for 23% of all female bladder cancer, whereas in men, 50% of the disease may be associated with cigarette smoking.

Incorporation in the regression equation of age at first exposure and years since cessation instead of smoking duration did not change the log-likelihood of the age- and sex-adjusted model. The magnitude of the reciprocal RRs for age at first exposure (RR = 1.02) and years since cessation (RR = 1.04) were similar to the RR for smoking duration (RR = 1.04). After adjusting for smoking duration, the RR per 10 cigarettes/day increment dropped from 1.3 (Table 2) to 1.2. After adjusting for smoking frequency, however, the RR per year of smoking (smoking duration) did not change. Cigarette smoking frequency, however, still contributed significantly to the log-likelihood of the model even after cigarette smoking duration was incorporated ($p < 0.01$).

Table 2. Incidence rate ratios (RR) for bladder cancer according to cigarette smoking features for men and women in categorical and continuous analyses; Netherlands Cohort Study 1986–1992

Cigarette smoking features	Cases in cohort	Person-years in subcohort	RR (95% CI)[a]
Never tobacco smoker[b]	55	7276	1.0 (ref.)
Status			
Ex	263	7001	2.1 (1.5–3.0)
Current	282	5664	3.3 (2.4–4.0)
Frequency (cigarettes/day)			
<5	30	1488	1.8 (1.1–2.9)
5–<10	59	1826	2.4 (1.6–3.7)
10–<15	87	2463	2.2 (1.5–3.3)
15–<20	93	1780	3.4 (2.3–5.0)
20–<25	120	2329	3.2 (2.2–4.7)
25+	115	1900	3.7 (2.5–5.4)
p-Value for linear trend			<0.01
Increment, 10 cigarettes/day			1.3 (1.2–1.4)
Duration (years)			
<10	10	632	1.4 (0.68–2.9)
10–<20	39	1592	1.8 (1.1–2.8)
20–<30	63	2506	1.7 (1.1–2.6)
30–<40	125	3213	2.7 (1.9–3.9)
40–<50	220	3807	3.4 (2.4–4.8)
50+	79	565	5.4 (3.5–8.5)
p-Value for linear trend			<0.01
Increment, 1 year			1.03 (1.02–1.04)
Age at first exposure (years)			
<15	140	2059	3.5 (0.39–5.2)
15–<17	143	2796	2.9 (0.98–4.2)
17–<19	108	3056	2.3 (1.6–3.3)
19–<21	79	1806	3.1 (2.0–4.6)
21–<25	33	1012	2.5 (1.5–4.0)
25+	33	1666	2.0 (1.3–3.3)
p-Value for linear trend			0.05
Increment, 1 year[c]			0.98 (0.95–1.0)
Years since cessation			
<1	295	5821	3.4 (2.5–4.7)
1–<10	112	2240	2.9 (2.0–4.3)
10–<20	71	2324	1.7 (1.1–2.5)
20–<30	54	1527	1.9 (1.2–2.9)
30+	11	723	0.81 (0.40–1.6)
p-Value for linear trend			<0.01
Increment, 1 year[c]			0.96 (0.95–0.98)
Inhalation			
No	95	3659	1.9 (1.3–2.8)
Yes	428	8610	3.1 (2.2–4.3)
Filter usage			
Filter-tipped	85	3374	2.6 (1.8–3.8)
Non-filter-tipped	314	6063	2.6 (1.9–3.8)

[a] Adjusted for age (years) and sex.
[b] Never smoked cigars, pipe, or cigarettes.
[c] Lifelong non-smokers were excluded from the continuous analysis.

The RRs for current *vs* ex-smokers, smoke inhalers *vs* non-inhalers, and users of non-filter-tipped cigarettes *vs* users of filter-tipped cigarettes dropped towards unity after adjustment for cigarette smoking frequency and duration. The RRs for men and women smoking <10, 10–<20, 20–<25, or >25 cigarettes per day were 0.75, 0.88, 0.73, 1.1, 1.0, and 1.2 compared with non-smokers after adjustment for age, sex, and smoking duration, respectively (p-trend = 0.02). The RRs for subjects smoking for a period of <10, 10–<20, 20–<30, 30–<40, 40–<50, or >50 years were 1.3, 1.5, 1.3, 2.1, 2.7, and 4.6 compared with non-smokers after adjustment for age, sex, and smoking frequency, respectively (p-trend < 0.01). Further adjustment for cigarette smoking status, inhalation, or filter usage did not change the results substantially.

Increasing daily tar and nicotine exposures were strong positively associated with bladder cancer risk in age- and sex-adjusted analyses, but weakly associated after adjustment for cigarette smoking frequency and cigarette smoking duration (Table 3).

Because almost no women reported ever smoking cigars or pipes, and men most commonly smoked cigars and pipes in combination with cigarettes, the RRs from cigar and pipe smoking compared with non-tobacco smoking were estimated for men only, adjusted for cigarette smoking (data not shown). Analyses for cigar and pipe smoking solely were not possible due to sparse data. Age confounded the association between cigar and pipe smoking and the risk of bladder cancer. The RR for cigar and pipe smoking indicated a statistically significant increased risk for cigar and pipe smokers. However, after additional adjustment for cigarette smoking frequency and duration, almost none of the estimated RRs for different cigar or pipe smoking characteristics remained statistically significant. The point estimates suggested that cigar and pipe smoking are not associated with an increased bladder cancer risk. Only the number of pipes smoked per day was positively associated with bladder cancer risk, although not statistically significant (p-trend = 0.17).

For passive smokers, age and sex appeared to be influential confounders. Exposure to ETS from spouses, parents, or work was not associated with an increased risk of bladder cancer among never tobacco smokers (Table 4). Furthermore, duration of exposure to environmental smoking in private and occupational settings combined did not appear to increase the risk of bladder cancer. Where the point estimates for parental and work-related ETS were above unity, the estimates for ETS from spouses and duration of exposure were lower. However, none of the presented RRs for ETS was statistically significant. All estimates were based on small numbers (Table 4).

Table 3. Adjusted incidence rate ratios (RR) for bladder cancer according to tar and nicotine exposure from ever cigarette smoking for men and women in categorical and continuous analyses; Netherlands Cohort Study 1986–1992

Tar/nicotine	Cases in cohort	Person-years in subcohort	RR (95% CI)[a]	RR (95% CI)[b]
Never tobacco smoker[c]	55	7276	1.0 (ref.)	1.0 (ref.)
Tar (mg/day)				
<100	45	1959	2.3 (1.4–3.5)	0.80 (0.40–1.60)
100–<200	68	1480	3.2 (2.1–4.9)	1.1 (0.53–2.3)
200–<300	73	1400	3.0 (2.0–4.6)	1.0 (0.46–2.2)
300–<400	46	902	3.1 (1.9–4.9)	1.0 (0.44–2.4)
400–<500	37	379	4.9 (2.9–8.5)	1.5 (0.61–3.8)
500+	52	632	4.5 (2.8–7.2)	1.7 (0.65–4.2)
p-Value for linear trend			<0.01	0.02
Increment, 100 mg/day			1.2 (1.1–1.2)	1.1 (0.93–1.3)
Nicotine (mg/day)				
<10	59	2417	2.2 (1.5–3.4)	0.78 (0.39–1.5)
10–<20	89	1700	3.5 (2.3–5.2)	1.1 (0.54–2.3)
20–<30	68	1278	3.1 (2.0–4.8)	0.94 (0.42–2.1)
30–<40	36	516	3.5 (2.1–6.0)	1.1 (0.47–2.5)
40–<50	18	267	3.4 (1.8–6.4)	1.0 (0.39–2.7)
50+	52	590	4.7 (3.0–7.6)	1.4 (0.57–3.6)
p-Value for linear trend			<0.01	0.08
Increment, 10 mg/day			1.1 (1.1–1.2)	1.0 (0.94–1.1)

[a] Adjusted for age (years) and sex.
[b] Adjusted for age (years), sex, cigarette smoking frequency (cigarettes/day), and cigarette smoking duration (years).
[c] Never smoked cigars, pipe, and cigarettes.

Table 4. Adjusted incidence rate ratios (RR) for bladder cancer according to environmental tobacco smoking among never tobacco smokers; Netherlands Cohort Study 1986–1992

Environmental tobacco smoking (ETS)	Cases in cohort	Person-years in subcohort	RR (95% CI)[a]
Partner smoking status			
Never	19	1484	1.0 (ref.)
Ex	18	2709	0.95 (0.46–2.0)
Current	11	2116	0.74 (0.29–1.9)
Parents smoking			
No	10	1212	1.0 (ref.)
Yes	42	5760	1.2 (0.56–2.4)
Work-related ETS			
Low	19	3097	1.0 (ref.)
High	21	2233	1.4 (0.70–2.6)
Duration exposure ETS (hours/day)[b]			
No exposure	18	1868	1.0 (ref.)
1–<3	13	1930	0.69 (0.33–1.4)
3+	10	1720	0.64 (0.29–1.4)
p-Value for linear trend			0.24
Increment, 1 hour/day			0.94 (0.86–1.0)

[a] Adjusted for age (years) and sex.
[b] In private and occupational settings combined.

Discussion

The results of this prospective cohort study strongly support a positive association between active cigarette smoking and bladder cancer risk in both men and women. Current cigarette smokers have an approximately three-fold higher risk of bladder cancer, and ex-smokers experience a two-fold increased risk. It appeared that associations of cigarette smoking characteristics with bladder cancer risk were largely attributable to cigarette smoking duration only; that cigarette smoking cessation, age at first exposure, and usage of filter-tips did not influence bladder cancer risk after adjustment of cigarette smoking frequency and duration; and that exposure to tar and nicotine weakly increased the risk of bladder cancer. Other types of smoking (*i.e.* cigar, pipe, or passive smoking) were not associated with an increased risk.

One strength of this and other prospective studies is that exposure was assessed before diagnosis of bladder cancer. Therefore, recall bias is not likely to have influenced our results. Furthermore, selection bias is not likely, because the follow-up of cases and subcohort members was almost complete [29, 37]. The relatively large number of bladder cancer cases in this study was an important strength.

Even though previous epidemiologic studies on cigarette smoking associated with bladder cancer (eight cohort and 35 case–control studies) differed in methodology, they consistently suggested a substantial increase in risk of bladder cancer for cigarette smokers [12]. A recent case–control study [38] concluded that the risk of bladder cancer may be higher in women than in men who smoked comparable amounts of cigarettes. The present study cannot confirm these findings. For all cigarette smoking features the RRs were similar for men and women.

The precise mechanism by which cigarette smoking causes bladder cancer has yet to be determined. It seems most likely that the risk of bladder cancer is related to some of the large number of compounds present in smoke. 2-Naphthylamine and 4-aminobiphenyl are the leading candidates as specific etiologic agents [4, 9, 10, 39, 40]. Several nitrosamines have also been shown to produce bladder cancer in animal models [10]. Tars induce bladder papillomas and carcinomas in mice [9]. However, this study suggests that smoking of low-tar and low-nicotine cigarettes with or without filter-tips does not reduce the risk of bladder cancer substantially after controlling for cigarette smoking status, frequency, and duration. To our knowledge, only one case–control study on the association between exposure to tars and bladder cancer risk [38], and no epidemiologic study on nicotine exposure, has been conducted previously. Castelao *et al*. [38] found no association for tar exposure in relation to risk after adjustment for frequency, duration, and currency of smoking. One other case–control study reported a diminution of risk from the smoking of light tobacco [41]. However, this risk estimate was not adjusted for cigarette smoking duration [41]. The calculation of tar and nicotine exposure from cigarettes might have been confounded by misclassification of the cigarette brand most commonly smoked if the validity of self-reporting for ex-smokers is lower than for current smokers. This might be possible because of recall bias [42]. However, the RRs for tar and nicotine exposure from cigarettes were comparable between ex- and current smokers. An alternative explanation for the reported weak association between exposure to tars and nicotine and bladder cancer risk is that the smoking of light and filter-tipped cigarettes is compensated by an increased puff volume, frequency and duration, interpuff interval, or volume and duration of inhalation [43, 44]. In the present study both frequency and duration of cigarette smoking were statistically significantly higher among smokers of filter-tip cigarettes.

The fact that cigarette smoking frequency and duration were consistently associated with an increased risk of bladder cancer in both categorical and continuous models suggests a direct positive dose–response association. In our dataset the men *vs* women RR decreased

from 6.7 (CI 5.3–8.5) to 3.5 (CI 2.7–4.6) after adjustment for these smoking factors. Furthermore, the fact that both age at first exposure and years since cessation of exposure have an influence in modifying the risk of bladder cancer might suggest that cigarette smoke contains both initiators and promoters for bladder carcinogenesis. However, it appeared that the associations of these cigarette smoking characteristics with bladder cancer risk could largely be explained by cigarette smoking duration. The statistically significant RRs for all cigarette smoking characteristics decreased substantially toward unity (and beyond) after adjustment for cigarette smoking duration. This would suggest that the promoting activity of cigarette smoke is of more importance that the initiating activity.

The evidence of an association between bladder cancer risk and other forms of tobacco use (*i.e.* cigar and pipe) is inconsistent and, when found, generally weaker than the association with cigarette smoking [4, 8, 10, 45]. Despite the plausibility of associations between cigar and pipe smoking and the risk of bladder cancer (since the smoke of both types of tobacco contains many of the same substance as that of cigarette tobacco), it has been suggested that their effect is likely to be small [14, 17, 46]. In our study almost all men smoked a cigar or pipe in combination with cigarettes; therefore we have adjusted the RRs for cigarette smoking frequency and duration to obtain less biased risk estimates for cigar and pipe smoking. Most RRs for cigar and pipe smoking were found to be lower than one after adjustment for cigarette smoking, which is probably an artefact of chance, since the CIs were rather large.

Data from experimental studies support the hypothesis that non-smokers might be exposed to potential carcinogens through the cigarette smoking of others [47]. Mutagens have been detected in the blood and urine of passive smokers [47, 48]. Therefore, it seems plausible to suggest that individuals exposed to ETS might be at increased risk of bladder cancer [17]. However, in two previous case–control studies no excess risk of bladder cancer due to ETS was demonstrated [17, 49]. According to Burch *et al.* [17], it is not likely that any association between passive smoking and bladder cancer will be strong, considering that the association between passive smoking and lung cancer also appears to be relatively weak. The present study adds to this body of evidence and endorses these earlier results. However, the findings are still preliminary and must be confirmed in other studies.

We conclude that active cigarette smoking is strongly associated with bladder cancer risk. Current cigarette smokers have an approximately three-fold higher risk of bladder cancer than non-smokers. Stopping smoking might be beneficial, although ex-smokers still experience a two-fold increased risk. In this study about half of male bladder cancer and one-fifth of female bladder cancer was attributable to cigarette smoking. Other types of smoking (*i.e.* cigar, pipe, or passive smoking) were not associated with an increased risk.

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